A proficiency testing scheme for the analysis of residual solvents in pharmaceutical products

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Introduction
Residual solvents in pharmaceuticals may be generally defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality based requirements.

Test material
A proficiency testing sample, for the quantification of residual solvents has been developed and introduced into the LGC PHARMASSURE scheme. The sample 2E - Residual solvents was provided on two occasions in the 2016/2017 scheme year, to customers in a number of countries worldwide.
The initial format of the sample was based on a ‘matrix’ and a spike solution.

Statistical evaluation
The assessment of participants was carried out using the robust mean (median) of the participant results to calculate the Assigned Value (AV) and the robust standard deviation of the participant results as the Standard Deviation for Proficiency Assessment (SDPA).

Good agreement was observed between the participant median result and the theoretical spike values, particularly for the class 1 solvents, which have allowable concentrations in pharmaceutical products of <10ppm.

Methodology
Figure 3: Pharmacopoeia procedures and analytical methods for the quantification of residual solvents.

Class 1 (solvents to be avoided) { • Benzene
• Carbon tetrachloride
• 1,2-Dichloroethane
• 1,1-Dichloroethene
• 1,1,1-Trichloroethane

Class 2 (solvents to be limited) { • Chloroform
• Hexane
• Methanol
• Toluene

Class 3 (solvents with low toxic potential) { • Acetone
• Ethanol

Ph. Eur. 2.4.24
USP 467
Ph. Eur. 2.2.28
GC-MS
GC-FID
Loss on Drying
Class 3 only

Table 1: Comparison of the participant median result and the theoretical spike values in PHARMASSURE round 60.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spike value (µg/g)</th>
<th>Median (µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>1.60</td>
<td>1.62</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>5.36</td>
<td>8.43</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>8.24</td>
<td>8.44</td>
</tr>
<tr>
<td>1,1-Dichloroethene</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>1281</td>
<td>1214</td>
</tr>
</tbody>
</table>

Conclusions
A feature of the residual solvent sample was a number of ‘non-analytical’ errors and truncated ‘less than’ results in the analytical data returned. Future developments to eliminate such data and the addition of ‘incurred, residual solvent’ matrix samples to the PHARMASSURE scheme is in progress for the next scheme year.